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Herbal And Polyherbal Formulation- An Approach Of Indian Traditional Medicinal System

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Abstract-
Indian traditional medicine system relies on herbs for Vedic time since the Indian peninsula is enriched with a variety of aromatic and medicinal plants because of variation in climate, soil, altitude, and latitude. The benefits of herbal therapeutics include easy availability and local beliefs over synthetic drugs. The thirst for natural and organic products is rising more and more because of a common belief that it has better effects with no side effects. Nowadays polyherbal medicines are becoming more popular as people look for natural remedies. In the traditional medicinal system, whole plants or mixtures of plants are utilized rather than isolated compounds. The polyherbal drugs aiming at different therapeutic targets are being favored and exercised by the modern medicine system to attain greater therapeutic efficacy and lesser toxicity. Polyherbal drugs have an edge over single herbal formulation due to synergism. The ethnopharmacological evidence and therapeutic efficacy of these formulations need to be established by scientific investigations and validated protocols before they appear into practice. The present review focuses on the significant features of herbal drugs and herb-herb combination. It also provides supportive evidence for their recognition as an established therapeutic approach.

Keywords- Herbal medicine, Synergism, Efficacy.

Introduction-

Approximately 80% population of developed countries and 60% of the world's population relies almost on plants for medicine and natural products (1,2). The literature resources reveal that about 15,000 plants are of medicinal importance, out of which 7,000-7,500 plants are being utilized by various communities to cure different diseases (3). Ayurveda, an Indian system of medicine, translates science into life to promote health rather than fight diseases, comprises 700 types of plants derived formulations. The classics of Indian literature on herbs include Rigveda, Atharvaveda (1500 to 1000 BC), Charak Samhita (1000 BC), and Sushruta Samhita (100 AD). Ayurvedic literature "Sarangdhar Samhita" (1300 AD) has pointed out the concept of polyherbal in the Indian medicinal system (4). Search for the history of phytotherapy is a search for the history of humanity itself. Classical herbal preparations, well known as ayurvedic preparation in Indian culture, reverse pathophysiological processes to stabilize 'doshas' which are identified as the regulatory factors for the maintenance of physiological processes of a living system, are known as ''yoga'' in Sanskrit (3). Traditional Indian medicinal system is entirely based on nature, herbs and polyherbal are becoming more popular throughout the world, with many chronic diseases responding to it well. Most peoples begin to take medications based on herbs as soon as their diagnoses are made, alongside conventional medicine in chronic diseases (5). Traditional systems of medicine often recommend complex

herbal mixtures and multi-compound extracts for the treatment of chronic and degenerative diseases of multifactorial origin, where one disease-one target-one drug seems not true (6). Nowadays medicines based on herbs are now widely accepted and there is a rise of interest in herbal remedies to cure diseases (7,8).
The technical terms brought by the European Medicines Agency (EMA), the World Health Organization, and renowned authors are given here to clear the picture relating to the herbal approach of medicine.

Herbs

The crude plant material like flowers, fruit, seeds, stems, leaves, wood, bark, roots, rhizomes, or other plant parts, which may be entire, fragmented, or powdered come under the definition of herbs (9).

Herbal substances/drugs

The herbal substances/drugs comprise the unprocessed, dried or fresh whole, fragmented or cut plants, plant parts, algae, fungi, lichen, and plant exudates that have not been specifically treated (10).

Herbal preparations/Herbal drug preparations

Herbal preparations/herbal drug preparations are comminuted or powdered herbal substances and preparations obtained by herbal substances for treatments such as extraction, distillation, expression, fractionation, purification, concentration, or fermentation of herbal substances. The tinctures, extracts, essential oils, expressed juices, and processed exudates are qualified as herbal preparations (10).

Genuine herbal preparations

Genuine herbal preparations include preparations without excipients but in the case of soft preparation like liquid herbal preparations, it may have solvents (10).

Herbal medicines

According to the (WHO), herbal medicines are “herbs and/or herbal materials and/or herbal preparations and/or finished herbal products that may contain, as active ingredients, parts of plants, other plant materials or combinations thereof in a form suitable for administration for patients”. As per the WHO definition, there are three kinds of herbal medicines: raw plant materials, processed plant materials, and medicinal herbal products. In some countries, herbal medicines may contain, by tradition, natural organic, or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials) (11).

The medicines which have plant materials either blended with chemically defined active substances or chemically defined isolated phytoconstituents do not come under the definition of herbal medicines (12). Herbal medicines are also referred to as botanicals or biomedicines (13).

Traditional medicine

It is the aggregate of the knowledge, skill, and practices grounded on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the upholding of health as well as in the prevention, diagnosis, improvement, or treatment of physical and psychological illness (11).

Indigenous traditional medicine

It is the aggregate of knowledge and practices, whether explicable or not, used in diagnosing, preventing, or eliminating physical, mental, and social illness. This knowledge or practice rests on experience and observation transferred orally or in writing from one generation to another. These practices should be native to the country where they are exercised (11).

Complementary medicine or alternative medicine

The health care practices that are not part of that country's own tradition or conventional medicine and are not fully incorporated into the dominating health care system of the country (14).

Conventional pharmaceuticals

These as medicinal drugs used in conventional systems of medicine for the treatment or prevention of disease or to restore, correct, or modify physiological conditions (11).

The different parts of a single herb may show different pharmacological actions that can be formulated into a variety of useful preparations. On the other hand, the desired pharmacological action of a herb may be either due to the synergistic action of different constituents or due to one of its active constituents. For example, the saponin glycoside of *Terminalia arjuna* ameliorates the inotropic effect and pumping activity of the heart and flavonoids are responsible for its vascular strengthening and antioxidant action (15).

Advantages of herbal medicines

To make herbal medicines more effective scientists try to extract biologically active compounds responsible for their main therapeutic effect but sometimes, not always, it leads to loss or reduction of their activity because the combination of a complex mixture of compounds of herbs has a greater effect than a single one. An example in the favor of this is *Kigelia pinnata*, where fractionation destroyed the previously observed cytotoxic effect. Another good example is the herbal shotgun approach of extracts of C*annabis Sativa* in producing contraction of human bladder than its main active constituent cannabidiol (16).
In comparison to synthetic drug molecules, natural products have more complexity, pleiotropic, multitargeted molecules, stereochemical richness, ring system diversity, and their pleiotropic nature help to perform many complementary tasks (17).
Phytochemicals can modulate or inhibit protein-protein interactions. Hence these molecules are worthwhile modulators of cellular processes such as the immune response, signal transduction, mitosis, and apoptosis (18,19).
Secondary metabolites of a plant may be more biologically active than individual ones or a random combination of them because they are part of biochemically related analogs, precursors, and catabolites of a particular biological system which can be considered as "mini combinatorial library", act synergistically. The synergism between molecules of a plant extract depends upon their simultaneous solubility with extracting solvent, and the multiplicity of targets (20) as shown in figure 1.

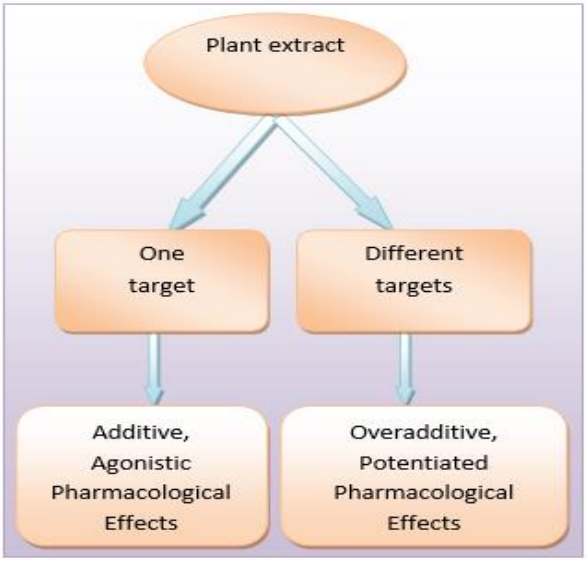

Figure 1: Mono and Multitarget effects of mono extracts with different constituents

Although the plant has milder antibiotic activity than commercially available antibiotics, it can potentiate the effect of commercially available antimicrobials as well as other herbs of similar effect.
Antibiotic resistance is a common problem nowadays either of their misuse or overuse, which can be minimized more economically by combining these antibiotics with suitable plants. The synergistic effects between herbal drugs and antibiotics against resistant bacteria provide a new and alternative way of treatment of resistant microbes. The microbes usually do not become resistant to herbs because herbs/whole extract/ active constituent may act synergistically with drugs to kill microbes, may inactivate/destroy enzymes produced by bacteria responsible for the degradation of antibiotics, and discourage the drug efflux system of bacteria making bacteria unable to excrete antibiotics from their body. Few of these synergistic effects are given in table 1 (17,21).

Table 1: Synergistic effect of antibiotics with phytochemicals

Serial number	Combination of Phytochemicals with Antibiotics	Observed effect
1.	Ethanolic extract of *Mangifera indica* with Tetracycline, Erythromycin	Reduction of the minimum inhibitory concentration (MIC) of Tetracycline and Erythromycin
2.	Methanolic extract of *Tectona grandis* with Tetracycline	Reduction of the MIC of Tetracycline
3.	Pseudolaric acid from *Pseudolarix kaempferi* Gordon with Fluconazole	Synergistic effect against several *Candida* species
4.	Soybean-derived genistein with Tamoxifen	Synergistic effect on the inhibition and growth of some breast cancer lineages

Herbal formulations have better patient tolerance, acceptance, and more economical than synthetic drugs. The herbal drugs have their origin in renewable sources (2,22). Herbal drugs also have a role in hormonal imbalance (23) and metabolic disorders (24).

Limitations of herbal medicines

All parts of the herbs are not equally beneficial. A certain part of a plant may be edible and another part may be poisonous. The root of rhubarb is used as a laxative and the stem is edible. However, its leaves are poisonous.
Herbs and pharmaceutical drug interaction may increase or decrease the pharmacological or toxicological effects of either component. These interactions are of special concern for the drugs like warfarin or digoxin having narrow therapeutic indices**.** Synergistic therapeutic effects may worsen the dosing of long-term medications. For example, traditional herbs used to reduce glucose concentrations in diabetes mellitus could theoretically precipitate hypoglycemia if taken with conventional drugs (25,26).
The renal poisoning credited to fang-ji (*Stephania tetrandra*) in a weight-loss preparation was caused by aristolochic acid (8) of guangfang-ji (*Aristolochia fangchi*). This issue reveals that misidentification is a serious concern for herbal medication.
The addition of pharmaceutical drugs to herbal products may lead to drug-herb interactions because of misidentification, adulteration, and contamination of herbs used to formulate the proposed product. The possibility of this interaction between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component (25).

The other limitations of herbal medicines can be summarized as follow (2,22).

- Ineffective in intensive medical care.
- Inadequate standardization and lack of quality control.
- Mistakes in nomenclature.
- Difficulties in identification of active phytochemicals.
- Complex nature of the mode of action.
- Herbal medicines take a longer time to show their effects than pharmaceutical drugs.

Safety issues of herbal drugs

It is a common belief that herbal drugs are very safe and free from side effects is not true. Herbs may also produce unwanted side effects and may be toxic. Herbs are usually less potent than synthetic drugs so the

adverse effects are relatively infrequent for most herbal drugs. Charak Samhita also wrote that polyherbal preparations have side effects when formulated inappropriately (3). The Food and drug administration (FDA) maintains and updates the list of herbs generally regarded as safe (GRAS) regularly (27).

Objections against herbal drugs

Herbal medicines are not widely accepted by the persons involved in prescription as it lacks safety, validation of efficacy, and quality regulations.

To resolve these issues, WHO has structured the guidelines and policies, ranging from the good agricultural and collection practices (GACP 2003), research methodologies, good manufacturing practices (GMP), relevant use of herbal medicine up to reporting of adverse reactions to ensure the quality, safety and efficacy of the herbal medicine. WHO has also furnished, "WHO Traditional Medicine Strategy 2014–2023" to encourage worldwide healthcare by incorporating traditional and complementary medicines. These guidelines address the variations in regulations of herbal medicines worldwide (14). Since 2004, herbal medicines are also food Drug Administration, FDA -regulated and defined as "complex extracts from a plant to be used for the treatment of disease." In India, herbal drug products constitute a major proportion of all the government recognized systems of health viz. Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy (AYUSH). Herbal remedies and medicinal plants which are to be incorporated in the modern system (Allopathic) must follow Drug Controller General of India (DCGI's) regulations (28).

In herbal medicines, the quantity of active constituents is too low to produce any relevant therapeutic effect. This assumption leads to a possibility to treat herbal medicine as placebos. This is not true as it is evident from various researches conducted on hypericum (29) for the treatment of depression, *Ginkgo biloba* extract for dementia (30), Saw palmetto extracts for the treatment of benign prostatic hyperplasia (31) concluded that plant extracts are significantly more effective than placebo.

Suggestions to improve the therapeutic effect of herbs and herbal medicines –

The phytoconstituents may vary according to the climate, soil type, and interactions with the environment. To get the herbal constituents of therapeutic effects plants must be cultivated in a climate that mimics the biotic and abiotic components of the wild as much as possible. Post-harvest processes include washing, drying, initial processing, and storage also decide the therapeutic value of herbal medicines supposed to be prepared. The inappropriate handling of *Valeriana officinalis* root oxidizes the valerenic acid decreases the yield of essential oil responsible for its activity (32). The activity is also reduced if the root is dried over 45^0C. It is summarized in figure 2.

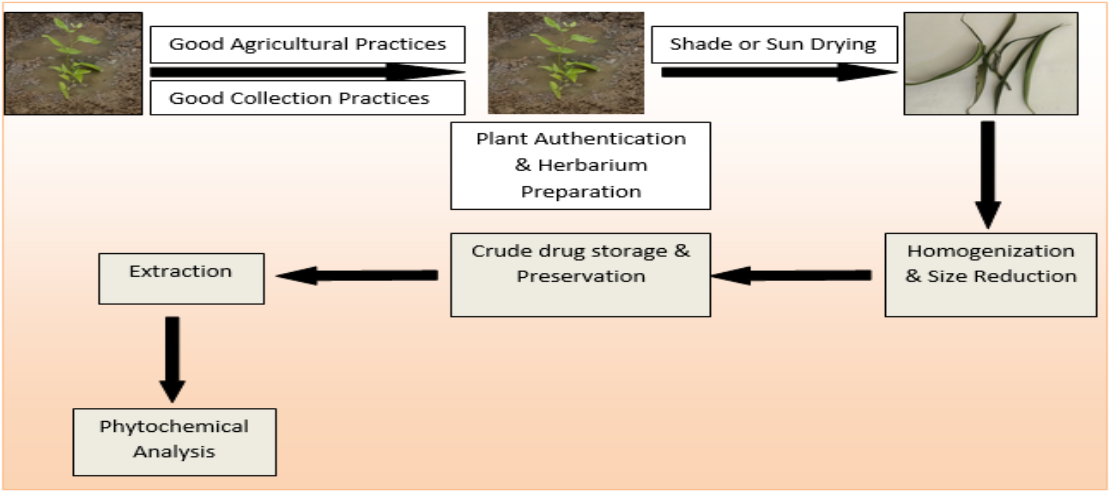

Figure 2- A layout of the pre-extraction process showing various steps able to deteriorate the quality of herbal medicines

A consistent chemical profile, the absence of contaminants, adulterants, and, consequently, desirable and reproducible therapeutic effects are ensured by the application of methods of standardization which in turn decides the ethical prescription of herbal medicines.

It is the need of time to develop new methods for pharmacological studies and clinical trials to evaluate the effects shown by a complex mixture of phytoconstituents (33). It is advocated to educate the medical students and physicians about the unique features of herbal medicines, their efficacy, and safety by the involvement of scientific methodology, free of prejudice.

Polyherbal formulations- Formulations having two or more than two herbs are called polyherbal formulation. Herb-herb combinations are also expressed as polyherbal therapy (3,4). In Ayurveda, most of the classical preparations are polyherbal, with a combination of 3 to 30 plants. The constituents of the polyherbal formulation are combined in a balanced and reproducible way. One or two constituents of the polyherbal combination will be active and the others will play a supporting role. the supporting herbs may help in proper absorption, transportation, and also contribute to reducing toxicity (5).

Advantages of polyherbal formulations over single herbal formulations-

It has been seen that certain pharmacological actions of herbs may be turned into therapeutic action only when potentiated by other plants, but not expressed when used alone.

Combinations of several medicinal herbs achieve a maximum therapeutic effect with minimum side effects. These effects are based on pharmacodynamic and pharmacokinetic synergism. The pharmacodynamic synergism is the regulation of absorption, distribution, metabolism, and elimination (ADME) of one herb by another herb. While in the case of pharmacodynamic synergism similar receptor or physiological is targeted by phytoconstituent with the same therapeutic activity.

The constituents of polyherbal formulation organized into certain formula show herb-herb interactions due to its diverse active principles through mutual enhancement, mutual assistance, mutual restraint, and mutual antagonism (4).

The use of a single herb may be suitable for the pathophysiological condition of some diseases. It may not fit for diseases with a multifactorial etiology, with a high incidence of resistance, or have a variable response to treatments, which are usually treated with polyherbal combinations aiming at multiple targets.

Polyherbal formulations ruled out the possibility of taking more than one different single herbal formulation at a time desired in few cases suits better patient compliance and therapeutic effect.

Most of them are effective even at a low dose and safe at a high dose, thus they have a superior risk to benefit ratio.

Limitation of polyherbal formulation

The polyherbal formulation may have better therapeutic potential than single herb extract but due to the diverse nature of its active principle, it may lead to incompatibility causing instability.

The major concern of a polyherbal formulation is its Clinical reproducibility which is tough to achieve for every batch of the polyherbal formulation. These batch to batch variations affect their efficacy and safety requires a need for change in the dosage regimen to get the desired therapeutic effect that is very cumbersome.

The toxicity studies and clinical trials on herbal formulations are not mandatory to get patents and manufacturing licenses for herbal formulations. The persons engaged in prescribing herbal preparations require no license to prepare medicines and follow quality control aspects based on their experience instead of using any guideline (34). Self-medication of polyherbal formulation with the allopathic drug is the common habit of few patients which may lead to negative aspects of possible drug-drug interactions (8).

Reason for compounding a polyherbal formulation (35)

There are various reasons in favor of compounding a polyherbal formulation are summarized as under.

- When the therapeutic effect of herbal medicine is supported and potentiated by the presence of different phytoconstituent, it becomes necessary to formulate polyherbal.
- Due to the broad therapeutic range, polyherbal shows a superior risk to benefit ratio.
- To widen the therapeutic window additional herbs may be added.
- Its formulation becomes obligatory in a case where a single herb formulation therapy fails to treat the strength and acuteness of an ailment.
- To nullify the toxic effect and to reduce the excessive potency addition of herbs of opposite nature becomes essential.
- To treat the harmful effect of a herb of the polyherbal formulation. Peppermint is added in senna formulation to treat cramp.
- An additional herb may be added to a herbal formulation to make the duration of action fast.
- To mask the unpleasant taste of a herbal formulation.
- Polyherbal is also prepared to enhance or extend the time of action of the leading herb.
- Polyherbal shows lesser side effects as compared to allopathic.

A few of the polyherbal formulations effective in various diseases are listed in table 2.

Table 2: Polyherbal formulation with their ingredients and different pharmacological activities

Commercial Name	Ingredients	Scientific evaluation	Reference
Immune-modulator against COVID-19			
Ayush Kwath	*Ocimum sanctum Linn, Cinnamomum zeylanicum Breyn., Zingiber officinale Rosc., Piper nigrum Linn*	Need to be established clinically	(36)
Anti-arthritic effect			
Arthosansar	*Commiphora wightii Arn, Boswellia serrata Roxb, Rasna Pluchea lanceolata, Ricinus communis Linn, Zingiber officinale, Shilajit* and *Withani somnifera Linn*	Complete Freund's adjuvant (CFA) induced arthritis in rats	(37)
Anti-inflammatory effect			
Upanaha Choornam	*Acorus calamus Linn., Anethum sowa Roxb, Cedrus deodara Roxb., Pluchea lanceolata DC Heirn /Alpania galangal Lance., Ricinus communis Linn., Nardostachys jatamansi DC Heirn*, *Sesamum indica Linn., Brassica campestris Linn., Dolichus biflorus Linn., Phaseolus mungo Linn., Phaseolus vulgaris Linn., Oryza sativa Linn., Panicum sumatrense Roth. & Schu., Aquillaria agallocha Roxh, Santalum alba Linn., Coleus vettiveroides KC Jacob., Sausserria lappa CB Cl, and Vettiveria zizinoides Linn***.,** Rock salt	TPA ((12-O-tetradecanoyl-phorbol-13-acetate) induced ear oedema in Swiss Albino mice	(38)
Polyherbal	*Calendula officinalis L., Lantana camara L. and Desmodium gangeticum Linn.*	Carrageenan induced paw edema model in albino rats	(39)
BHUx	*Commiphora mukul, Terminalia arjuna, Boswellia serrata, Semecarpus anacardium and Strychnos nux vomica*	Carrageenan-induced rat paw edema model	(40)
Triphala	*Emblica officinalis Gaertn, Terminalia belerica Linn., Terminalia chebula Retzr.*	Adjuvant-induced arthritis in mice	(41)
Antigenotoxic effect			
Septilin	*Balsamodendron mukul , Sank Bhasma , Maharasnadi qoath, Tinospora cordifolia, Emblica officinalis, Moringa pterigosperma, Glycyrrhiza glabra*	Micronucleus (MN) and sperm shape abnormality assays in Swiss albino mice	(42)
Anti-cancer effect			

Polyherbal	*Tecomella undulate, Bauhinia variegate, Oroxylum indicum, Indigofera tinctoria*	MTT (3-(4,5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) assay on cell lines of human colon adenocarcinoma and human breast adenocarcinoma	(43)
Antibacterial effect			
Ya-Samarn-Phlae	*Garcinia mangostana, Oryza sativa, Curcuma longa, and Areca catechu*	Clinical and Laboratory Standards Institute (CLSI) broth microdilution	(44)
Anti-microbial effect			
Polyherbal gel	*Azadirachta indica, Curcuma longa, Allium sativum, Ocimum sactum, Cinnamomum zeylanicum nees and Tamarindus indica*	Agar well diffusion technique against *S. aureus, B. subtilis, A. niger* and *E. coli*	(45)
Shrishadi	*Albezzia lebbeck, Cyprus rotandus and Solanum xanthocarpum*	Disc diffusion method	(46)
Hepatoprotective effect			
Hepax	*Plumbago zeylanica, Picrorrhiza kurroa, Piper nigrum, Zingiber officinale*, *Phyllanthus emblica, Terminalia chebula*, Sodii carbonas impura, Calcii oxidum and Potassii carbonas impure	Carbon tetrachloride (CCl 4), Paracetamol and Thiocetamide induced hepatotoxicity in rats	(47)

Conclusions

In the Indian traditional system of medicine, substances of natural origin whether whole plants, parts of plants, animal parts, or minerals are used either alone or in combination.

It is very conclusive that the formula of the polyherbal formulation may be achieved by combining, 1) leading herbs with similar pharmacological actions to improve the therapeutic effects (reinforcement approach), 2) assisting herbs aiming at secondary symptoms (potentiating approach), 3) assimilating herbs to enhance the ADME (pharmacokinetic approach), 4) herbs to counterbalance the effect of the main drug (restraint, detoxification, and antagonistic approach) in an appropriate ratio to treat and prevent the complex chronic disease of polysymptomatic nature. Herbal medicines are widely accepted but evidence-based development of standardized phytomedicine may fill the gap that has become wider in the last few years.

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